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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,678	05/01/2007	Kathryn E. Uhrich	01435.035US1	8472

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EXAMINER	
ORWIG, KEVIN S	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,678	UHRICH ET AL.	
	Examiner	Art Unit	
	Kevin S. Orwig	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-23,88,240 and 241* is/are pending in the application.

4a) Of the above claim(s) *88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 8-23, 240 and 241* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. The arguments filed on May 18, 2010 have been entered.

Status of the Claims

Claims 1, 2, 8-23, 88, 240, and 241 are pending. Claims 3-7, 24-87, and 89-239 were previously cancelled. Claim 88 is withdrawn. No claims have been amended; no claims have been added. Claims 1, 2, 8-23, 240, and 241 are now under consideration. This Office Action is in response to the request for continued examination filed on May 18, 2010.

OBJECTIONS/REJECTIONS MAINTAINED

The rejection of claims 1, 2, 8-23, 240 and 241 under 35 U.S.C. 103(a) over TIAN and UHRICH is maintained as discussed below.

Claim Rejections - 35 USC § 103 (Maintained)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 8-23, 240 and 241 are rejected under 35 U.S.C. 103(a) as being unpatentable over TIAN (Tian *et al.* Polymer Preprints (2002) 43(2); 719-720; of

record) in view of UHRICH (WO 03/005959; Published Jan. 23, 2003; 2nd reference on IDS dated Nov. 17, 2006, of record) (hereinafter '959).

1. Tian discloses amphiphilic molecules of the structure depicted in formula III of instant claim 22 (elected species) that form stable polymeric micelles (p. 719, left col., 2nd par.; Scheme 1; 1st par. of Results and Discussion section). Tian teaches that these molecules are intermediates in the preparation of amphiphilic star-like macromolecules (ASMs) (2nd par. of Introduction). Tian teaches that these micelles have hydrophobic cores suitable as "microcontainers" for lipophilic compounds and that the hydrophilic/lipophilic ratios (HLB) can be controlled by changing the length of the PEG or acyl chains (first pars. of Introduction and Results and Discussion sections). Tian teaches that the micelles form 20 nm diameter aggregations (i.e. nanoparticulates).

2. While Tian discloses the molecules of applicants' elected species, and suggests that they have utility for the encapsulation of hydrophobic compounds, Tian does not explicitly teach the use of these compounds to remove low-density lipoproteins (LDL) or to treat atherosclerosis. Since Tian does not specifically disclose what types of molecules may be encapsulated within the micelles, one would be motivated to look to the related literature for guidance regarding their usage.

3. Uhrich discloses polymeric compounds that form stable micelles in solution, wherein the micelles have a hydrophobic core and act as microcontainers for lipophilic compounds (abstract; 1st par. on p. 2). Just as the molecules of Tian, the hydrophobicity of Uhrich's compounds can be controlled by changing the length of the PEG or acyl chains (2nd par. on p. 34). Uhrich teaches that these micelles are

particularly useful for solubilizing hydrophobic molecules (p. 26, 1st par.; and p. 34, last par.). Uhrich teaches the use of these compounds to sequester lipoproteins such as LDL that contribute to atherosclerosis (page 10, 4th par., elements (a) and (c)) by administering them to a patient in need of reducing the concentration of lipoproteins (p. 10, end of 4th par.). Uhrich teaches that such administration can minimize cardiovascular diseases, such as atherosclerosis, caused by the presence of excess LDL in the blood (p. 10, end of 4th par.).

4. Uhrich discloses embodiments of the compounds wherein they may contain the molecules taught by Tian (i.e. the instantly claimed molecules) as a part of their structure. For example, see Scheme 2 (top of p. 26), which discloses non-PEGylated versions of the instantly claimed molecules. It is noted that Uhrich teaches the use of polyethylene glycol (i.e. PEGylation) with these molecules (p. 29, 2nd par.). Additionally, Figure 10 teaches an embodiment wherein four of Tian's molecules are incorporated into a polyol core, the only difference from Tian's compounds being that the embodiment depicted in the figure contains an amide instead of an ester linkage between the mucic acid moiety and the mPEG moiety. It is noted that replacement of this amide by an ester is taught in Uhrich's disclosure (see description of the compounds on pages 2-8, particularly embodiment d) on p. 7, and the description of R^4 in this embodiment on p. 8). Thus, consistent with Tian's teaching, Tian's molecules are intermediates in the ASMs of Uhrich.

5. Given the similarity of the micelles formed by each of these molecules, and their identical intended uses to encapsulate hydrophobic compounds, it would have been

prima facie obvious to one of ordinary skill in the art at the time of the invention to utilize the molecules of Tian to treat atherosclerosis by sequestering or removing LDL as taught by Uhrich. One would have been motivated to do so since Tian suggests that the molecules are suitable for use with hydrophobic compounds, but does not teach which specific compounds are suitable. Thus, the ordinary artisan would have readily envisioned the use of Tian's intermediates in the same manner as the macromolecular ASMs of Uhrich. Further, the artisan would be motivated to use Tian's molecules since they are simpler than those of Uhrich and therefore would be easier and cheaper to prepare. The similarity of the micelles and use of both Tian's intermediates and Uhrich's ASMs would have provided the artisan with a high expectation that Tian's molecules would function in a substantially similar way and be useful in the treatment of atherosclerosis by sequestering LDL in the hydrophobic core. This is especially true given the direct teachings of both Tian and Uhrich that micelles of each of the disclosed compounds function in the same way, namely forming aggregates suitable to carry lipophilic compounds. Thus, claims 1, 2, 8-23, 240, and 241 are obvious over Tian and Uhrich.

Regarding the obviousness rejections herein, it is noted that a reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of

the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, in the absence of evidence to the contrary, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

Applicants' arguments have been fully considered but are not persuasive. Applicants assert that they have not argued the references individually, stating "Indeed, the Applicants have specifically argued that Uhrich does not provide the teaching and suggestion the use of the compounds claimed in present application for the removal of LDL and/or the treatment of atherosclerosis *and*, in conjunction with the Examiner's concession that Tian does not disclose the use of the disclosed compounds for LDL removal or treatment of atherosclerosis, the rejection should be withdrawn" (response, p. 6-7).

However, this argument, like those put forth previously, amounts to a statement of the deficiencies of the individual references and fails to appreciate the combined teachings of the references, and what they suggest to one of skill in the art . As detailed in the prior Office Action, and reiterated above, the *combination* of Tian and Uhrich renders the claims obvious for the reasons of record.

Applicants discount the need for evidence to rebut the *prima facie* case of obviousness that has been established. Applicants instead assert that because the molecules of Tian are linked by a (small) core molecule in Uhrich, an artisan would

appreciate that the linkage would change the conformation and behavior in solution of the Tian molecules (response, p. 7).

This argument continues to ignore the fact that both Tian and Uhrich teach that the molecules, both the intermediate "monomers" of Tian and the covalently linked "polymeric" forms of Uhrich, are taught to function in *precisely the same way*, forming stable micelles in solution that have a hydrophobic core and act as microcontainers for lipophilic compounds. Thus, the express teachings of Tian and Uhrich directly refute applicants' assertion. Since Tian directly teaches that the non-polymerized molecules form micelles capable of transporting lipophilic compounds (just like those of Uhrich), a skilled artisan would understand that it is the amphiphilic portions (i.e. Tian's molecules) themselves that are responsible for the sequestration of the hydrophobic compounds (i.e. per Tian's Scheme 1) rather than a small polyfunctional core that is present merely to link several of the amphiphilic compounds together. One would clearly have a reasonable expectation of success in using Tian's molecules for the same purposes as those described for the polymerized versions of Uhrich.

Applicants refer to Uhrich at p. 34, lines 21-22, asserting that Uhrich teaches that it is the core that forms the hydrophobic microenvironment that encapsulates small hydrophobic molecules (response, p. 7).

However, applicants' argument is misplaced because the core referred to by Uhrich at p. 34, lines 21-22 is not the same "core" that links the molecules of Tian together, which is what applicants are referring to in their argument. What Uhrich actually states at p. 34, lines 21-22 is:

> "The PEG arms of the polymers of the present invention thus form a hydrophilic shell that solubilizes the polymer in water, while the core forms a hydrophobic microenvironnment that encapsulates small hydrophobic molecules."

Thus, in context, it is clear that Uhrich indicates that the core is everything *but* the PEG chains. In fact, this exact arrangement is directly taught by Tian (see Scheme I, where the PEG chains form a hydrophilic external shell and the rest of Tian's molecule forms a hydrophobic microenvironment that encapsulates the drug), further illustrating the functional similarities between the molecules of both Tian and Uhrich.

Applicants argue that the requirement to demonstrate the functional part of the molecule is the small polyfunctional core is arbitrary, and that applicants only need to show why the combination of Uhrich and Tian is improper (response, p. 8).

Applicants only need to demonstrate that the function of the small polyfunctional core (the core in Uhrich that links the intermediate molecules of Tian together) outweighs that of the rest of the molecule if they wish their previous arguments to be persuasive. It is not a requirement. However, it is not arbitrary because, based on the teachings of Tian and Uhrich (see above), applicants' arguments are not persuasive in the absence of such evidence. As to applicants' burden to show that the combination of Tian and Uhrich is improper, the examiner agrees that if applicants were to show that this combination of references was improper, the rejections should be withdrawn. However, applicants have not shown why the combination of Tian and Uhrich is improper. Thus, the rejections of record are maintained.

Conclusion

Claims 1, 2, 8-23, 240, and 241 are rejected. No claims are currently allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached Monday-Friday 7:00 am-4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached Monday-Friday 8:00 am-5:00 pm at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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